

H-FIB: Adjunctive Renal Denervation to Modify Hypertension and Sympathetic  
Tone as Upstream Therapy in the Treatment of Atrial Fibrillation

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## **PROTOCOL**

### **H-FIB:**

# **ADJUNCTIVE RENAL DENERVATION TO MODIFY HYPERTENSION AND SYMPATHETIC TONE AS UPSTREAM THERAPY IN THE TREATMENT OF ATRIAL FIBRILLATION (HFIB)**

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## 1. ABBREVIATIONS

AAD	Anti-arrhythmic drugs
ACC	American College of Cardiology
ACT	Activated Clotting Time
AE	Adverse Event
AF	Atrial Fibrillation
AFEQT	Atrial Fibrillation Effect on Quality-of-Life
AFL	Atrial flutter
AHA	American Heart Association
ALT	Alanine transaminase
ARBs	Angiotensin receptor blockers
ARDS	Acute Respiratory Distress Syndrome
AST	Aspartate aminotransferase
AV	Atrioventricular
BNP	Brain natriuretic peptide
BP	Blood Pressure
BSA	Body surface area
CABG	Coronary artery bypass grafting
CFAE	Complex fractionated atrial electrograms
CHF	Congestive heart failure
CMC	Clinical Management Committee
CT	Computerized tomography
CTI	Cardiac Troponin I
CV	Curriculum Vitae
CVP	Central Venous Pressure
DC	Direct current
DCC	Data Coordinating Center
DSMB	Data Safety Monitoring Board
EAC	Event Adjudication Committee
ECG	Electrocardiogram
eCRFs	Electronic Case Report Forms
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
EP	Electrophysiology
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HRS	Heart Rhythm Society
ICU	Intensive Care Unit
INR	International Normalized Ratio
IRB	Institutional Review Board
I/O	Input/Output

InCHOIR	International Center for Health Outcomes & Innovation Research
JNC-7	Joint National Committee 7
LA	Left atrium
LAA	Left atrial appendage
LBBB	Left bundle branch block
LMW	Low molecular weight
LV	Left ventricle
LVEF	Left ventricular ejection fraction
MACE	Major adverse cardiac event
MDRD	Modification of Diet in Renal Disease
MI	Myocardial infarction
MR	Mitral regurgitation
MRI	Magnetic resonance imaging
MV	Mitral valve
NIHSS	National Institutes of Health Stroke Scale
NYHA	New York Heart Association
PCI	Percutaneous coronary intervention
PV	Pulmonary vein
OHRP	Office of Human Research Protections
OR	Operating Room
QoL	Quality of Life
RBC	Red blood cells
RF	Radiofrequency
RVAD	Right Ventricular Assist Device
SAE	Serious Adverse Event
SF-12	Short Form – 12
SSL	Secure Socket Layer
ST-T	ST segment/T wave
SVC	Superior vena cava
TDI	Tissue Doppler Imaging
TEE	Trans-esophageal echocardiography
TIA	Transient Ischemic Attack
TTE	Trans-thoracic echocardiography
UADE	Unanticipated adverse device effect
UP	Unanticipated Problem
URL	Upper Reference Limit

## 2. ABSTRACT

<b>Objectives</b>	Determine the role of adjunctive blood pressure management and sympathetic modulation attained via renal sympathetic denervation in the prevention of AF recurrence in patients with hypertension scheduled for an AF ablation procedure. Patients will be randomized to either AF catheter ablation (usual therapy) or AF catheter ablation plus renal sympathetic denervation.
<b>Study Design</b>	Prospective, placebo-controlled, double-blind, randomized (1:1) clinical trial; patients randomized to either catheter ablation (control group) or a catheter ablation + renal denervation (study group).
<b>Target Population</b>	History of documented significant hypertension (defined as SBP $\geq$ 160 mm Hg and/or DBP $\geq$ 100 mmHg) and receiving treatment with at least one anti-hypertensive medication, or a known history of hypertension and receiving treatment with at least two anti-hypertensive medications (specifically for hypertension).
<b>Rx arms</b>	AF catheter ablation alone versus AF catheter ablation plus renal sympathetic denervation
<b>Sample Size</b>	<b>Total:</b> 300 patients: provides 80% power to detect a 40% decrease in AF recurrence (24% versus 40%) (measured at 12 months) This study is divided into two phases: an initial PILOT phase (to include 50 patients) followed by the remaining 250 patients to a total of 300 patients. The PILOT phase will be conducted at up to 10 US sites. An interim safety analysis will be conducted when all patients in the PILOT phase (50 subjects) have completed the 3-month follow up visit. The purpose of this analysis is only for safety. The efficacy/outcome data for the primary endpoint will <u>not</u> be examined; this will permit pooling these 50 patients with the subsequent 250 patients for the final efficacy analysis.
<b>Duration</b>	24 months follow-up following randomization.
<b>1° Endpoints</b>	Single-procedure freedom from AF recurrence off all AADs (after the 90 day blanking period) at 12 months.
<b>2° Endpoints</b>	AAD-free single-procedure freedom from AF recurrence 24 months (not-including recurrences within the first 90 days of the initial ablation procedure); freedom from AF recurrence at 24 months (not-including a 90 day blanking period) despite taking AADs; blood pressure control between the two groups as compared to baseline at t = 6 months, 12 months and 24 months; Major Adverse Cardiac Events (MACE); differences in measures of LV hypertrophy (LV wall thickness, mitral inflow parameters, LV mass index <sup>2,7</sup> ) and LA size recorded via TTE at baseline and at 12 months for each patient; procedure adverse events; total number of anti-hypertensive medications at study end, compared between the 2 treatment arms; QOL.
<b>Inclusion Criteria</b>	Age $\geq$ 18; history of AF and planned for a catheter ablation procedure; history of hypertension and on at least one anti-hypertensive medication; accessibility of renal vasculature (as determined by intra-procedural renal angiography); Ability to understand the requirements of the study; Willingness to adhere to study restrictions and comply with all post-procedural follow-up requirements
<b>Exclusion Criteria</b>	Inability to undergo AF catheter ablation (e.g., presence of a left atrial thrombus, contraindication to all anticoagulation); Prior left atrial ablation for an atrial arrhythmia (before this index procedure); NYHA class IV congestive heart failure; Individual has known secondary hypertension; Individual has renal artery anatomy that is ineligible for treatment including: a) Inability to access renal vasculature, b) Main renal arteries < 3 mm in diameter or < 20 mm in length., c) Hemodynamically or anatomically significant renal artery abnormality or stenosis in either renal artery which, in the eyes of the operator, would interfere with safe cannulation of the renal artery or meets standards for surgical repair or interventional dilation, d) History of prior renal artery intervention including balloon angioplasty or stenting that precludes a possibility of ablation treatment; Individual has an estimated glomerular filtration rate (eGFR) of less than 45mL/min/1.73m <sup>2</sup> , using the MDRD calculation; Individual has a single functioning kidney (either congenitally or iatrogenically); Individual is pregnant or nursing; Life expectancy <1 year for any medical condition

**Table 1. Schedule of Treatments and Tests**

	Baseline	Procedure	Discharge	3, 6, 12, 18 & 24 mos	Event Driven
<b>Type of visit</b>	Office	Hospital		Office	
<b>Informed Consent</b>	X				
<b>Brief History &amp; Physical</b>	X		X	X	
<b>Office BP Measurement</b>	X			X	
<b>Medications</b>	X		X	X	
<b>Blood chemistry</b>	X			6 & 12 mo only	
<b>Quality-of-Life Assessment</b>	X			12 & 24 mo only	
<b>TTE <sup>φ</sup></b>	X			12 mo only	
<b>ECG</b>	X				X
<b>Continuous ECG Monitoring (7 days each)</b>				3 mo, 6 mo, 12 mo, 24 mo only	
<b>Renal Doppler</b>				6 mo only	
<b>Blinding assessment</b>				12 mo only	
<b>Randomization*</b>		X			
<b>Hospital Admission</b>		X			X
<b>EP Mapping &amp; AF Ablation</b>		X			X
<b>Renal Angiography</b>		X			X
<b>Renal Sympathetic Denervation <sup>§</sup></b>		X			
<b>Adverse Events</b>					X
<b>AF recurrence</b>					X
<b>Missed Visit Assessment</b>					X
<b>Mortality</b>					X
<b>Study Completion/Early Termination</b>					X

<sup>φ</sup> Performed within 3 months of randomization (i.e., within 3 months of the planned ablation procedure).

\* Randomization will occur after renal angiogram.

<sup>§</sup> The blinding of the patient is maintained by the fact that the renal angiogram and renal denervation steps will be performed with the same sedation as used for the ablation procedure: either deep sedation or general anesthesia (per the usual protocol of the EP laboratory).

### 3. OBJECTIVES

#### **Purpose of the Study**

The objective of the H-FIB trial is to determine the role of renal sympathetic denervation in the prevention of Atrial Fibrillation (AF) recurrence in patients with hypertension for whom a catheter-based AF ablation procedure is planned. Patients will be randomized to either AF catheter ablation (usual therapy) or AF catheter ablation plus renal sympathetic denervation.

#### ***3.1 Primary Hypothesis***

In hypertension patients with atrial fibrillation, there is ample evidence of a strong association between the chronic hypertension and arrhythmia-inducing cardiac substrate modifications; the association seems related to both hypertension itself (along with derangements in the renin-angiotensin-aldosterone system), and elevated sympathetic tone. It is hypothesized that a treatment strategy targeting both these ancillary conditions (hypertension and elevated sympathetic tone) and atrial fibrillation triggers themselves may lead to greater and more durable procedural success post-catheter ablation. In hypertensive patients undergoing catheter ablation for AF, we hypothesize that there will be a difference through 12 months between the two treatment arms in AAD-free freedom from recurrent AF after a 90 day blanking period following a single AF ablation procedure. The null hypothesis of principal interest is that there will be no difference through 12 months between the two treatment arms in single-procedure freedom from AF off of all AADs after a 90 day blanking period in patients randomized to AF ablation with a single renal sympathetic denervation procedure compared to patients randomized to AF ablation alone.

#### ***3.2 Secondary Aims***

1. Compare AAD-free single-procedure freedom from AF recurrence through 24 months (not-including recurrences within the first 90 days of the initial ablation procedure)
2. Compare freedom from AF recurrence through 24 months regardless of antiarrhythmic drug (AAD) use (excluding the 90 day blanking period)
3. Examine blood pressure control between the two groups as compared to baseline at 6 months, 12 months and 24 months
4. Examine differences between treatment groups in measures of LV hypertrophy (LV wall thickness, mitral inflow parameters) and LA size by TTE at baseline and at 12 months for each patient
5. Procedure-related adverse events
6. Major Adverse Cardiac Events (MACE)
7. Serious Adverse Events
8. Compare anti-hypertensive medication use in the two treatment arms at 24 months.
9. Compare quality of life between treatment arms and differences in quality of life from baseline using a disease specific scale (AFEQT) at 12 and 24 months.

## 4. BACKGROUND

There is a wealth of epidemiological, pre-clinical and clinical data that suggests that both hypertension and sympathetic overdrive have important effects on the cardiovascular system that increases the propensity for atrial fibrillation. Furthermore, there is pre-clinical and early clinical data that indicate that this relationship can be modulated by catheter-based renal sympathetic denervation (by virtue of its effects on both the renin-angiotensin-aldosterone system and sympathetic tone). The following details some of these preliminary data which provides the scientific basis for this proposed HFIB clinical trial.

### **Hypertension and Atrial Fibrillation**

Aside from its obvious impact on renal function, chronic hypertension significantly increases the risk for stroke, coronary artery disease, heart failure, and vascular disease, and is believed to mediate the pathogenesis and progression of atrial fibrillation (AF) via its remodeling effects on cardiac anatomy. This inextricable link between hypertension and cardiovascular health has been well described, as has their combined effect on up to 40% of the aging, obesity-battling Western world.

Furthermore, from the perspective of a cardiovascular electrophysiologist, the prevalence of hypertension has important implications for the prognosis of patients with cardiac arrhythmias—particularly, drug-resistant AF. Despite significant advances in the field of catheter ablation for AF, the prevailing evidence suggests that even when procedural success can be obtained acutely, a considerable rate of PV electrical reconnection is observed over time. This is further supported by a 15–50% rate of clinical AF recurrence during follow-up; and as demonstrated by several recent studies which have extended follow-up to 6 years, clinical recurrence is even more likely with increasing scrutiny and duration of follow-up.

The situation is more complicated for patients with persistent AF—the treatment of which has been less effective with PV isolation alone. Although the pathogenesis is not completely understood, hypertension is believed to mediate the pathogenesis and progression of paroxysmal to persistent AF, via its remodeling effects on cardiac anatomy. This includes left ventricular hypertrophy, impaired ventricular filling, left atrial enlargement, and alteration of atrial electrophysiology. It is therefore reasonable to assume that limiting or reversing such morphological changes could have a profound effect on the effectiveness and durability of currently available ablative therapies for AF. Indeed, there is a substantial (albeit at times, a conflicting) body of evidence suggesting that treatment with “positively” remodeling agents (such as antagonists of the renin-angiotensin system) may decrease AF recurrence in patients after cardioversion or as adjunctive treatment with antiarrhythmic drugs.

Renal sympathetic denervation is a therapeutic modality that has been shown to affect the sympathetic state in various pre-clinical and clinical disease states. While Symplicity HTN-3 was overall a negative study for the control of resistant hypertension, there are

compelling data suggesting that one of the most important reasons for the negative outcome was technical: namely, the inability of point-by-point radiofrequency ablation to achieve circumferential denervation of the peri-renal sympathetic fibers. To this point, as opposed to the initial (and somewhat crude) spot radiofrequency ablation catheter employed in that trial, there are now a number of other renal denervation systems specifically designed to safely deliver a circumferential array of ablative lesions (that in pre-clinical animal models, is very effective in achieving excellent renal denervation).

### **Potential Role of renal sympathetic denervation as an adjunct therapy in the treatment of AF: Potential benefits beyond BP control.**

Multiple pre-clinical and clinical studies have demonstrated that the sympathetic nervous system (SNS) plays an important role in the initiation and maintenance of AF, especially in patients with any degree of structural heart disease<sup>3,4</sup>. Increases in sympathetic tone frequently precede the onset of AF<sup>5,6,7</sup>, and excessive sympathetic nervous activation (assessed by <sup>123</sup>I-mIBG scintigraphy) can predict recurrences of AF after catheter ablation<sup>8</sup>. One explanation for the ‘pro-fibrillatory’ effects of the sympathetic nervous system is the distribution of cardiac autonomic innervations. The PV-LA junction has abundant sympathetic innervations, which become the dominant sites for the origin of focal atrial tachyarrhythmias in response to heightened sympathetic tone<sup>9</sup>. Low concentrations of tyramine, which activates sympathetic neurons by releasing norepinephrine from nerve endings, can initiate spontaneous AF by early after-depolarization-mediate triggered activity from the LA-PV junction<sup>11</sup>. Following catheter ablation, or rapid atrial pacing, the PV-LA junction can undergo further neural remodeling (i.e. sympathetic hyperinnervation), potentially making these sites even more sensitive to adrenergic stimuli<sup>11,12</sup>. The importance of the autonomic nervous system in mediating AF is further strengthened by the results of interventions intended to inhibit sympathetic outflow to the heart. Low-level vagus nerve stimulation, which suppresses stellate ganglion nerve activities, significantly reduces the frequency of paroxysmal atrial tachyarrhythmias in ambulatory canines<sup>13</sup>. This excessive sympathetic nervous activation, which contributes to the pathogenesis of atrial fibrillation, is a potential target of renal sympathetic denervation, beyond just the control of blood pressure.

An additional consideration is the effect of renal sympathetic denervation on cardiac structure and function. In patients with essential hypertension, increased left ventricular mass (LVM) is an independent predictor of both AF and cardiovascular outcomes. Furthermore, reductions in LVM are associated with prognostic benefits, independent of reductions in blood pressure<sup>14,15</sup>. To this end, Brandt and colleagues recently demonstrated that renal sympathetic denervation significantly reduced LVM and improved diastolic function; two established risk factors for the development and maintenance of AF<sup>16</sup>. Interestingly, even in a small group of BP ‘non-responders’, there was marked reductions on LVM and improvements in diastolic parameters. Regression of LVM during antihypertensive therapy is associated with a lower likelihood of new-onset AF, independent of blood pressure lowering and treatment modality in essential hypertension<sup>17</sup>. In total, these studies suggest that renal sympathetic denervation has the

potential to reduce the frequency of AF recurrences in patients with significant essential hypertension who are undergoing catheter ablation of AF.

Furthermore, there is now a substantial body of pre-clinical data demonstrating that in animal models, renal denervation has profound effects on both atrial electrophysiology and atrial ultrastructure (decreasing fibrosis). And as a consequence, renal denervation has favorable effects on AF initiation and duration in animal models of AF.

### **Preliminary Data & Rationale for this Study**

A single-center randomized controlled trial examined the effects of adjunctive renal denervation in a group of patients with resistant hypertension and atrial fibrillation<sup>18</sup>. In this study, 27 patients were enrolled, 14 were randomized to AF ablation only and 13 were randomized to AF ablation with renal artery denervation. Nine of the 13 patients (69%) treated with PVI with renal denervation were AF-free at the 12-month post-ablation follow-up examination versus 4 (29%) of the 14 patients in the PVI-only group ( $p = 0.033$ ). While this was admittedly a small study, and included the unusual population of patients with *both* AF and resistant hypertension, it nonetheless was the proof-of-principle that adjunctive renal denervation can have potent antiarrhythmic effects.

Furthermore, a more recent study examined the link between sympathetic system overdrive and atrial arrhythmogenesis, *independent* of hypertension control.<sup>19</sup> In this study of patients undergoing catheter ablation of AF, the investigators tested whether moxonidine, a centrally-acting sympathoinhibitory agent, can similarly lead to a reduction in post-ablation AF recurrence. In this prospective, double-blinded study, 291 hypertensive patients were randomized to receive either moxonidine (0.2-0.4 mg daily) or placebo, along with standard antihypertensive treatment. Despite the fact that there were *no significant differences in blood pressure* between the two groups, the 12-month AF recurrence rates were 36.9% in the AF ablation alone group and 20.0% in the AF ablation + moxonidine group ( $p=0.007$ ). This study provides additional clinical proof-of-principle that modification of the sympathetic system would provide ameliorative anti-arrhythmic effects post-AF ablation even without significant effects on the blood pressure.

Finally, we conducted a pilot H-FIB study (FDA IDE# G120025) which revealed interesting outcomes. This single-blind, multicenter (10 sites) study enrolled patients with a history of significant hypertension (defined as a SBP  $\geq 160$  mmHg and/or DBP  $\geq 100$  mmHg) and receiving treatment with at least one anti-hypertensive medication, and scheduled to undergo AF ablation. After AF ablation, patients were randomized to no further therapy or renal denervation using an off-the-shelf radiofrequency ablation catheter (Celsius Thermocool, Biosense-Webster, Inc). Briefly, 13 patients were randomized to AF ablation + renal denervation (study group) and 17 patients to AF ablation only (control group). After a mean of 15 months of follow-up, freedom from AF was achieved in 77% (10/13) of the study group compared to 53% (9/17) of Controls. While not statistically significant, these data are nonetheless quite compelling. However, there were significant safety events that prompted us to halt the study: 3 patients with

renal artery dissection, and 3 patients with significant post-ablation renal artery stenosis (>60%). Thus, while the off-the-shelf ablation catheter had been safe in our single-center experience, we were not able to replicate these favorable safety results in the multicenter study. Together, these data suggest that the H-FIB study should be re-started utilizing a dedicated renal denervation catheter.

To this point, the **H-FIB trial** will re-start using the Vessix renal denervation system. Patients meeting the inclusion / exclusion criteria will undergo a catheter ablation procedure for AF according to the standard practice. During the procedure, they will additionally undergo a renal angiogram to assess the accessibility of the renal vasculature. Assuming that the anatomy is suitable for renal denervation, the patient will be randomized to receive either: (1) AF ablation + catheter-based renal sympathetic denervation, or (2) AF ablation alone. Both groups will be followed for two years.

The primary endpoint is single-procedure survival free from AF (without taking AADs) through 12 months, with a 90 day blanking period. The **H-FIB** trial will be conducted in up to 20 participating sites in the United States and Europe (10 sites for the initial 50 patients). The aim of **H-FIB** is to assess the potential therapeutic and quality-of-life benefit of performing hypertension-associated cardiac substrate modification, in addition to the standard practice of catheter ablation of atrial fibrillation. It is believed that because both hypertension and sympathetic overdrive both independently (and likely synergistically) allow for the genesis and/or propagation of atrial fibrillation, significantly reversing and/or reducing the effects of such atrial remodeling by renal denervation will improve the durability of procedural success after an ablation.

## 5. SPECIFIC AIMS

### *5.1 Primary Endpoint*

#### **Efficacy**

The primary endpoint of this study is AAD-free single-procedure freedom from AF recurrence through 12 months (not including a 90 day blanking period).

### *5.2 Secondary Endpoints*

***AAD-free single-procedure freedom from AF recurrence through 24 months (not-including recurrences within the first 90 days of the initial ablation procedure).***

***Freedom from AF recurrence through 24 months (not-including the pre-defined 90 day blanking period) despite taking AADs.***

***Blood pressure control between the two groups as compared to baseline at 6 months, 12 months and 24 months.***

***Major adverse cardiac events (MACE)***

- defined as a non-weighted composite score of: death, stroke, CHF hospitalization, clinically diagnosed thromboembolic events other than stroke and hemorrhage requiring transfusion within 12 months of randomization

***Serious Adverse Events******Differences in measures of LV hypertrophy (LV wall thickness, mitral inflow parameters) and LA size******Procedure adverse events******Total number of anti-hypertensive medications at study end, compared between the two treatment arms******Quality of Life*****6. STUDY DESIGN**

This is a prospective, multi-center, double-blinded, randomized trial. The trial will be conducted in up to 20 clinical sites from both within and outside the United States, for a total of 300 randomized patients. During the enrollment of the initial 50 patients, the number of sites will be 10. Accrual is expected to take 24 months, and all patients will be followed for 24 months post randomization.

**7. RANDOMIZATION**

All patients who have given informed consent for the study will undergo catheter ablation for AF, as this is the standard care they would receive regardless of enrollment in the study. During the procedure, a renal angiogram will be performed to assess the accessibility of the renal vasculature, and its appropriateness for catheter-based renal sympathetic denervation. If the renal anatomy meets the protocol defined dimensions, the patient will then undergo randomization.

Patients will be randomized to one of two treatment groups:

- Group 1: catheter ablation of atrial fibrillation plus renal sympathetic denervation
- Group 2: catheter ablation of atrial fibrillation (control group)

Patients will be randomized in a 1:1 fashion. By this arrangement, 50% of the patients will undergo renal sympathetic denervation (Group 1) and 50% will not (Group 2). All patients will undergo AF catheter ablation.

### **Randomization Procedure**

A DCC representative will be available to discuss any questions regarding patient eligibility. Once the site investigator has confirmed that the patient meets all eligibility criteria for participation in the trial, and has completed the eligibility forms in the Electronic Data Capture (EDC) system, randomization will be performed electronically. Randomization to the study assignment will be generated by the EDC system once the checklist of inclusion and exclusion criteria has been completed and verified. For the purpose of the primary analysis, patients are considered enrolled in the study once they have signed informed consent.

## **8. MASKING**

The operating physician will be aware of the randomization assignment, but the patient will not. The blinding of the patient is maintained by the fact that the renal angiogram and renal denervation steps will be performed with the same sedation as used for the ablation procedure. This is typically either deep sedation or under general anesthesia (per the usual protocol of the EP laboratory); this amount of anesthesia used for the AF ablation procedure is sufficient for the discomfort felt during the renal denervation procedure. This approach has been selected to minimize (1) study bias and (2) placebo effect. The randomization schema will be blocked by size for each site. Core labs will also be blinded to treatment assignment. Adverse events will be adjudicated by an Event Adjudication Committee and trial oversight will be provided by an independent DSMB. Those assessing the primary outcome will be blinded to patients' treatment assignment.

## **9. STUDY POPULATION**

### **Characterization of Patient Population**

The patient population for this trial consists of patients with atrial fibrillation and a history of hypertension. All patients should be planned for a catheter ablation procedure for atrial fibrillation. All patients who meet the eligibility criteria may be included in the study regardless of gender, race or ethnicity.

### **Inclusion Criteria**

1. Age  $\geq$  18 years of age
2. History of AF (paroxysmal or persistent) and planned for a guideline-supported catheter ablation procedure
3. History of significant hypertension (defined as SBP  $\geq$ 160 mm Hg and/or DBP  $\geq$ 100 mmHg) and receiving treatment with at least one anti-hypertensive medication,  
*or*  
Clinical History of hypertension and receiving treatment with at least two anti-hypertensive medications (specifically for blood pressure reduction)
4. Renal vasculature is accessible as determined by intra-procedural renal angiography.

5. Ability to understand the requirements of the study
6. Willingness to adhere to study restrictions, comply with all post-procedural follow-up requirements and to sign informed consent

### **Exclusion Criteria**

1. Inability to undergo AF catheter ablation (e.g., presence of a left atrial thrombus, contraindication to all anticoagulation)
2. Prior left atrial ablation for an atrial arrhythmia (before this index procedure)
3. Patients with NYHA class IV congestive heart failure
4. Individual has known secondary hypertension
5. Individual has renal artery anatomy that is ineligible for treatment including:
  - a. Inability to access renal vasculature
  - b. Main renal arteries < 3 mm in diameter or < 20 mm in length.
  - c. Hemodynamically or anatomically significant renal artery abnormality or stenosis in either renal artery which, in the eyes of the operator, would interfere with safe cannulation of the renal artery or meets standards for surgical repair or interventional dilation.
  - d. A history of prior renal artery intervention including balloon angioplasty or stenting that precludes a possibility of ablation treatment.
6. Individual has an estimated glomerular filtration rate (eGFR) of less than 45mL/min/1.73m<sup>2</sup>, using the MDRD calculation.
7. Individual has a single functioning kidney (either congenitally or iatrogenically).
8. Individual is pregnant or nursing.
9. Life expectancy <1 year for any medical condition

### **Recruitment Strategies**

Recruitment strategies may include: mailings to referring physicians of the study hospitals, symposia and health care events targeted towards this population; as well as telephone calls to neighboring health care facilities. The DCC will regularly assess actual enrollment in relation to pre-specified goals, and additional interventions to increase enrollment will be implemented as needed. The Screening Log will identify numbers of patients screened and reasons for non-enrollment in the trial.

### **Roll-in phase**

Each site has the option of enrolling two patients as part of a roll-in phase. Each roll-in patient will have AF ablation, renal angiography and renal sympathetic denervation performed. Patient data on these roll-in patients will not be used for the final analysis.

- Roll-in patients will be required to sign the study ICF, but will not be randomized.
- Although the data will not be used for the primary analysis, patients will asked to adhere to the same follow up schedule of visits as randomized patients.

- As per FDA, roll-in patients will count toward the enrollment ceiling.
- The CRF must be adjusted to clearly reflect roll-in patients from randomized patients.

## 10. TREATMENT INTERVENTIONS

### Catheter Ablation for Atrial Fibrillation

- The approach to catheter ablation of AF should be performed according to the EP lab standards. A few general comments (and restrictions) are noted below:
- Patient anesthesia will be administered according to standard EP lab protocol.
- Arterial and venous access will be achieved through cannulation of the right and/or left femoral arteries and veins as per the usual practice of the treating electrophysiologist.
- Full systemic anticoagulation will be instituted as per standard hospital procedures to a target ACT of approximately 300 seconds or greater (or equivalent level depending on testing system performed). As per the most recent AF consensus document <sup>20</sup>, pre-procedural anticoagulation management should include performing the ablation on therapeutic oral anticoagulation – e.g.,: warfarin with a goal INR 2-3, or one of the newer oral anticoagulants: dabigatran, rivaroxaban, apixaban, or edoxaban (either continuing one of these agent to the time of the procedure, or discontinuing it 3 to 5 days prior to ablation, followed by periprocedural bridging using low-molecular-weight heparin). These recommendations apply to the cardiac ablation. Consistent with the Symplcity-1 and -2 trials, there are no specific additional recommendations pertaining to pre-procedural anticoagulation prior to or following renal sympathetic denervation.

Patients in the study will include patients with paroxysmal AF and non-paroxysmal AF. The AF ablation procedure will be performed with any catheter approved for that such specific indication or per clinical practice at the study site for that indication (i.e., for non-paroxysmal AF).

For US and OUS sites, a list of recommended catheters is in Appendix V. OUS sites may use catheters which have been approved in their jurisdiction for that indication.

- **All Patients:** Pulmonary vein isolation with an approved irrigated radiofrequency ablation catheter, laser ablation or cryoballoon ablation catheter (as per the usual practice of the treating physician). PV isolation must be confirmed by a multi-electrode mapping catheter after placing the last ablation of the PV-isolating lesion set.

➤ **Paroxysmal AF Patients:**

- Additional ablation may be performed to target non-PV triggers
- SVC isolation is permitted (as per the physician's usual practice)

- A typical flutter CT isthmus line may be placed in patients with either a history of ECG-determined typical flutter or induced typical flutter during the procedure
  - One should not perform additional targeting of CFAE sites or the placement of linear lesions
- **Non-Paroxysmal AF Patients:**
- This category includes all patients with AF sustained for  $\geq 7$  days, and requiring termination by pharmacological or electrical cardioversion
  - Additional ablation may be performed to target non-PV triggers, SVC isolation, linear lesions (e.g., CT isthmus line, Mitral Isthmus line, Roof line)
  - Additional targeting of rotor activity using approved mapping technology is permitted
  - Ablation of CFAE sites is not permitted
- As per usual practice of the treating physician, an approved catheter navigation system (such as the robotic or magnetic navigation system) may be employed for AF ablation.
  - During radiofrequency ablation, power titration should be performed as per the physician's usual practice to avoid thromboembolic complications or perforation. One reasonable strategy includes careful power titration to achieve an impedance drop not exceeding 10%. In general, the tip temperature should not exceed 45°C, and preferably should stay below 42°C.
  - During cryoballoon ablation, ablation lesions should be placed as per usual practice (2-4 min lesions/PV). During ablation of the right pulmonary veins, as per the center's usual practice, a strategy should be used to minimize the possibility of phrenic nerve injury. Two examples of such appropriate strategies include: i) pacing the phrenic nerve from the SVC during ablation and monitoring of diaphragmatic excursion to indicate phrenic nerve integrity, and ii) monitoring diaphragmatic excursion with free breathing during ablation to indicate phrenic nerve integrity.
  - During laser ablation, the CardioFocus HeartLight Catheter must be used according to the guidelines set in the FDA approved Instructions for Use <sup>21</sup>. Phrenic nerve pacing is recommended to avoid injury to the phrenic nerve. As per the IFU, one method for conducting pacing is to pace from the superior vena cava once the Balloon is inflated near the right superior pulmonary vein (RSPV) and if desired, the right inferior pulmonary vein (RIPV) to assess the location of the phrenic nerve by observing any "capture" at the target energy delivery site. It is advised that pacing be conducted at high output to ensure capture of the phrenic nerve. When pacing prior to energy delivery, the site of diaphragmatic stimulation (and therefore the approximate phrenic nerve location) can be

compared via fluoroscopy or ICE with the target energy delivery site. Energy should not be delivered to any area where there is phrenic nerve capture. Alternatively, concomitant phrenic nerve pacing can be performed using a pacing catheter in the SVC during laser balloon energy delivery to the RSPV (or RIPV). When used, energy delivery must be discontinued if movement of the diaphragm slows or changes during energy delivery.

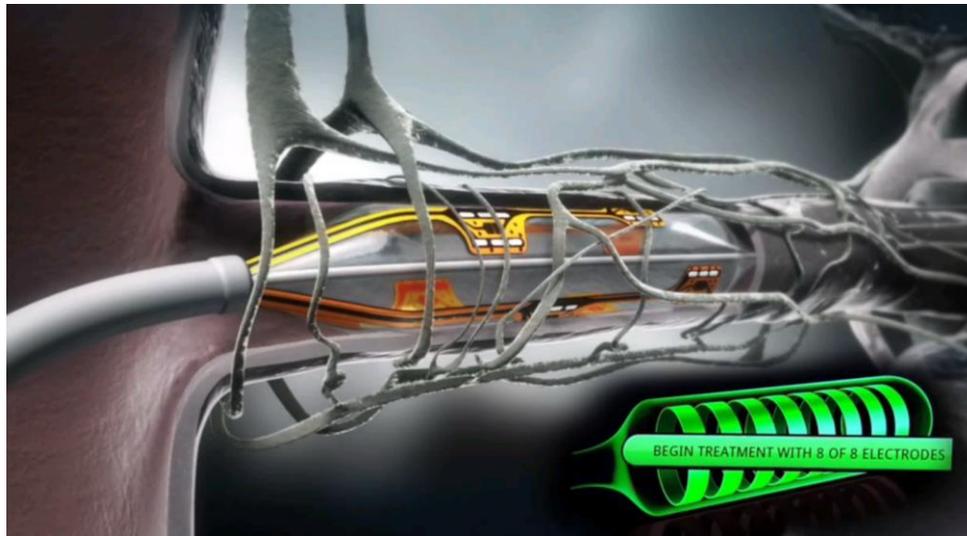
- During the ablation, an intravenous heparin infusion will be maintained for a target ACT >300 seconds. ACTs should be monitored every 30-60 minutes (per usual practice).

### **Renal Angiography**

- A renal angiogram will be performed *after* the AF ablation procedure is complete. Once the renal arteries are found to be acceptable for ablation, randomization will occur. Once angiography is performed, no additional atrial ablation is permitted.
- Following completion of the cardiac ablation and renal angiography, if the patient was randomized to the control group, the heparin infusion will be discontinued. The arterial and venous sheaths will be removed and hemostasis achieved with manual pressure (protamine may be used to facilitate this) and/or percutaneous vascular closure devices (as per the institution's practice). If the patient was randomized to the renal sympathetic denervation arm (study group), these steps will be performed after the renal artery ablation has been completed.

### **Renal Sympathetic Denervation**

- After confirmation of eligibility, the radiofrequency ablation catheter will be introduced into each renal artery.
- Despite some variability in renal vascular anatomy, the method for performing the procedure is fairly straightforward. An aortogram is performed to visualize the renal vessels and deem suitability (no significant renal artery stenosis or atherosclerosis, etc.).
- The renal ablation procedure will be performed using the Vessix™ Renal Denervation System (Boston Scientific, Quincy, Massachusetts). The operating physician will manipulate the ablation catheter into the renal arteries as per standard operating procedures.



- The Vessix catheter is available in various sizes, and can be used to treat arteries between 3 mm and 7 mm in diameter and more than 20 mm in length. Radiofrequency energy is delivered via 8 electrodes to four distinct sites within the artery in a bipolar fashion. As with other renal denervation procedures, this catheter delivers four lesions in the artery which are separated along the length of the artery and are also separated orthogonally in different planes (anterior, inferior, posterior, and superior).
- The Vessix generator is pre-programmed with a temperature-controlled treatment algorithm. Energy is delivered to achieve a temperature of 68°C. Treatment time is 30 seconds. Average power is approximately 1 watt per electrode and is displayed on the generator screen during treatment. The system is designed to automatically deliver the proper amount of energy to achieve the appropriate temperature. The user does not need to (nor can he/she) adjust or set any of the biophysical parameters when using this system. The generator uses a proprietary algorithm (including impedance measurement) to determine appropriate apposition with the vessel wall. Electrodes which do not have appropriate apposition (such as those extending into the aorta) are automatically disabled by the generator.
- Only one catheter placement is required in most renal arteries. If the operator determines that the initial placement is unsatisfactory to treat the full length of the artery, a second activation will be permitted in a different location. No more than two full catheter activations will be allowed in each renal artery; however, if a lesion is terminated early (i.e., in <15 sec), then an additional ablation lesion is permitted to compensate for this.
- After delivery of a complete lesion (30 seconds), no further testing is required to ensure renal denervation. Physiologic endpoints for renal denervation have not been standardized.

### Post-procedure Hospitalization

- As per usual practice, post-ablation patients will be admitted overnight to a telemetry unit for monitoring. ECG recordings will be obtained from all patients.

If intracardiac echo was not used during the procedure (and at procedure end) to assess for pericardial effusion, patients will undergo trans-thoracic echocardiography to assess for pericardial effusion.

### **Anticoagulation**

- As per the ACC/AHA/HRS Guidelines on AF ablation, systemic anticoagulation should be administered to the patient for a minimum of 2 months after the procedure. Options include:
  1. Warfarin: for a target INR 2-3.
  2. One of the novel Thrombin or Factor Xa inhibitors
  3. LMW heparin formulations (such as Fragmin/Lovenox) injected subcutaneously
- As per the ACC/AHA/HRS Guidelines on AF ablation, long-term management of anticoagulation should be according to the baseline risk status for embolic stroke

### **Blanking Period and Second Procedures**

- The duration of the blanking period for all patients is 90 days.
- All Class I and III antiarrhythmic drugs should be stopped no later than 90 days after ablation of paroxysmal and non-paroxysmal AF patients. The use of any Class I or III AADs after the 90 day blanking period will be considered a primary failure.
- Any repeat AF ablation will cause the patient to be considered a primary failure.
- No repeat renal denervation procedures will be allowed.

### ***Risks and Benefits***

Pre-clinical <sup>22</sup> studies using similar lesion location and lesion duration parameters demonstrated no evidence of clinically significant adverse renal artery damage/stenosis. Our protocol utilizes an average power of 1 watt per electrode.

## **11. DEFINITIONS AND MEASUREMENT OF ENDPOINTS**

### ***11.1 Primary Endpoint***

#### ***Efficacy***

The primary endpoint of this study is AAD-free freedom from AF recurrence through 12 months (not including the pre-defined 90 day blanking period). This will be defined by absence of any electrocardiographically documented AF, clinically documented AF or AF determined by Holter monitoring.

- Patients who die prior to the 12-month assessment will be considered as treatment failures (not free from AF).

- The use of any Class I or III AADs after the 90 day blanking period will be considered a primary failure.

### ***11.2 Secondary Endpoints***

***AAD-free single-procedure freedom from AF recurrence through 24 months (not-including recurrences within the first 90 days of the initial ablation procedure).***

Recorded at the 12 and 24 month visits for each patient.

***Freedom from AF recurrence through 24 months (not-including the pre-defined 90 day blanking period) despite taking AADs.***

Freedom from AF recurrence will be defined by absence of any electrocardiographically documented AF, clinically documented AF or AF determined by Holter monitoring.

- Patients who die prior to the 12-month assessment will be considered as treatment failures (not free from AF).

***Blood pressure control between the two groups as compared to baseline at 6 months, 12 months and 24 months.***

Determined by office visit blood pressure readings.

***Differences in measures of LV hypertrophy (LV wall thickness, mitral inflow parameters) and LA size***

Recorded via TTE at baseline and at 12 months for each patient.

### ***Serious Adverse Events***

#### ***Major Adverse Cardiac Events***

- Major adverse cardiac events (MACE) defined as a non-weighted composite score of: death, stroke, CHF hospitalization, clinically diagnosed thromboembolic events other than stroke and hemorrhage requiring transfusion within 12 months of randomization

***Total number of anti-hypertensive medications at study end, compared between the two treatment arms***

Recorded at the 24 month visit for each patient.

### ***Quality of Life***

The change in QoL from baseline to 12 months will be measured using one quality of life instrument (AFEQT). The AFEQT is a 20-item disease-specific scale developed to capture subjective ratings of AF disease and treatment burden. The AFEQT questionnaire can be found in Appendix II. *For this trial, the AFEQT is available in English, Spanish, French, German, and Czech. Inability to read and complete the instrument in the available languages does not preclude a patient from enrollment in the trial.*

### **11.3 Safety**

#### **Adverse Events**

The incidence of serious adverse events over the course of the trial will be compared between the two treatment groups. All serious and all protocol-defined adverse events (AE) will be adjudicated by an Event Adjudication Committee (EAC). The endpoints for safety will be reported as the frequencies of occurrence of each adverse event, the rate of adverse events per patient/year and time to each event. In addition, the number of patients with each serious adverse event type will be recorded. Safety data will be collected throughout this study and the incidence of each event type will be computed along with the 95% confidence intervals.

*An adverse event (AE) is any undesirable experience (sign, symptom, illness, abnormal laboratory value, or other medical event) occurring to a subject during the course of the study. Physical findings (including vital signs) observed at follow-up, or pre-existing physical findings that worsen compared to baseline, are adverse events if the investigator determines they are clinically significant.*

*AF recurrence by itself is considered a recurrence of disease (pre-existing condition), and, therefore, does not meet the definition of an AE.*

*Recurrence of pre-existing AFL/AT is also considered recurrence of disease, and does not meet the definition of an AE.*

*The following clinical events will not be considered an adverse event for this clinical study:*

- *Minor pericarditis attributable to the ablation procedure defined as pleuritic chest discomfort with or without pericardial rub and ECG changes.*

- *AF/AFL/AT recurrence requiring pharmacological or synchronized electrical cardioversion during the hospitalization for the index ablation procedure, or throughout the duration of the study. However, new onset of left atrial flutter occurring post-ablation is an AE.*
- *Re-ablation for AF or pre-existing AFL/AT*
- *Standard follow-up or exacerbation of pre-existing conditions unrelated to the cardiovascular system including diabetes, cancer/tumors, multiple sclerosis, allergies, osteoporosis, arthritis, emphysema, vision or aural problems and rectal polyps.*
- *Physical trauma determined to be unrelated to the ablation or renal sympathetic denervation procedures including pain due to musculoskeletal injuries, muscle aches due to over-exertion, joint degeneration, tendonitis and bursitis and burns from external causes.*
- *Newly developed disease or illness unrelated to AF, the ablation or renal sympathetic denervation procedures, a study device or the drugs used to treat cardiovascular illness including gastrointestinal ulcers, hemorrhoids, immune system deficiencies like HIV or AIDS, infectious diseases like hepatitis or herpes viruses, neurological/psychological disorders such as Alzheimer's, Parkinson's, dementia, obsessive/compulsive or eating disorders.*
- *Other illness, if clearly isolated from the cardiovascular disease, including jaundice unrelated to systemic infection, infection in extremities unrelated to the procedure, bacterial infection or cellulitis.*
- *Common ailments unrelated to the cardiovascular system, the ablation or renal sympathetic denervation procedures, a study device or the drugs used to treat cardiovascular illness including common headache, muscle pain, food poisoning, superficial infections, rashes, warts, shingles, constipation, eczema, hernias, upper respiratory infections or influenza.*

### **Serious Adverse Event**

*A serious adverse event (SAE) is any event that meets one or more of the following criteria:*

- *Leads to a death*
- *Leads to a serious deterioration in the health of a subject that resulted in:*
  - *a life-threatening illness or injury*
  - *a permanent impairment of a body structure or a body function*

- *in-patient hospitalization or prolongation of an existing hospitalization\**
- *medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function*
- *Leads to fetal distress, fetal death or a congenital abnormality or birth defect.*

***This definition excludes hospitalization solely due to arrhythmia recurrence or non-medically urgent cardioversion.***

*\*Planned hospitalization for a condition present prior to the participant's enrollment in the study will not meet the definition of an SAE. An AE would meet the criterion of "hospitalization" if the event necessitated an admission to a health care facility (e.g., an overnight stay). Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes.*

### **Unanticipated Serious Adverse Event**

An unanticipated (unexpected) serious adverse event is any serious adverse event that is not protocol-defined or documented in the patient consent form. Expedited reporting is required for serious adverse events that are unexpected.

### **Unanticipated Adverse Device Effects**

An unanticipated adverse device effects (UADE) is any serious adverse effect on health or safety or any life-threatening problem caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan, or any other unanticipated serious problem associated with the device that relates to the rights, safety, or welfare of subjects.

### **Unanticipated Problems**

According to the Office for Human Research Protections (OHRP), an Unanticipated Problem (UP) generally includes any incident, experience, or outcome that meets **all** of the following criteria: (1) Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied; *and* (2) Related or possibly related to participation in the research (in this guidance document, *possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been

caused by the procedures involved in the research); *and* (3) Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Based on the definitions above and as illustrated below (per OHRP guidance), many adverse events are not unanticipated problems, and many unanticipated problems are not adverse events. However, some adverse events are also unanticipated problems. For example, a serious adverse event that is unexpected and at least possibly related to study participation is also by definition an unanticipated problem. As stated above, an unanticipated problem may not necessarily be an adverse event, which is the case when the problem does not cause actual physical harm to participants. For example, if a laptop computer with sensitive, identifiable study data is stolen, this theft places the participants at greater *risk* of psychological or social harm; this is an unanticipated problem that is not an adverse event. Another example of an unanticipated problem that is not an adverse event is if the FDA announces that one of the study drugs is tainted (e.g., with paint chips), yet no participant experiences any adverse effects.

### **Event Recording**

The following adverse events will be captured throughout the period of trial participation:

- Protocol-defined (as described below)
- Serious unanticipated events (serious “*Other*” adverse events)

### **Causality**

The investigator will assess the relationship of an adverse event to the intervention. The investigator should distinguish the relationship between the event and (a) ablation procedure (i.e. AF ablation procedure or other concomitant procedures), and (b) renal sympathetic denervation. Causality will be defined as follows:

#### *Probable*

Adverse events that, after careful medical evaluation, are considered with a high degree of certainty to be related to the intervention (AF ablation ± renal sympathetic denervation). The following characteristics will apply:

- A reasonable temporal relationship exists between the event and the intervention, and
- The event is a known reaction to the intervention, and cannot be explained by an alternative etiology commonly occurring in the population/individual.

#### *Possible*

Adverse events that, after careful medical evaluation, do not meet the criteria for a probable relationship to the intervention, but for which a connection cannot be ruled out with certainty. The following characteristics will apply:

- The event occurs after intervention, and
- The event is not a known reaction to intervention, but cannot be explained by a commonly occurring alternative etiology

*Unlikely*

Adverse events that, after careful medical evaluation, do not meet the criteria for a possible or probable relationship to intervention and for which a connection is unlikely. The following characteristics will apply:

- The event does not follow a reasonable temporal sequence from administration of the intervention, or
- May have been produced by environmental factors, and there is no apparent pattern of response to the intervention.

**Reporting of Serious Adverse Events and Unanticipated Adverse Device Effects**

All investigators must report both expected (protocol-defined) and unexpected SAEs. All protocol defined SAEs must be reported directly to the clinical center's IRB and the DCC within 10 business days of knowledge of the event, or as dictated by the specific IRB policy, whichever is sooner. All deaths, UADEs, and unexpected SAEs that are possibly or probably related to the renal sympathetic denervation must be reported to the DCC and the clinical center's IRB within 24 hours of knowledge of the event, or as dictated by the specific IRB policy, whichever is sooner. All *unexpected SAEs* that are **unlikely related to the study intervention** must be reported to the DCC and the clinical center's IRB within **5** business days of knowledge of the event, or as dictated by the specific IRB policy, whichever is sooner.

The DCC will report these events to the DSMB chair within 72 hours of notification. All SAEs will be reported to the DSMB at least semi-annually, at the discretion of the DCC medical monitor.

**Reporting of Unanticipated Problems**

All *UPs* that are also SAEs, which are at least possibly related to the study intervention, must be reported to the DCC within 24 hours of knowledge of the event. All *UPs* that are not SAEs must be reported to the DCC within 5 calendar days of knowledge of the event, or as dictated by the specific IRB policy, whichever is sooner.

**DCC Reporting to FDA**

The DCC will report unexpected SAEs that are possibly or probably related to the investigational device or UADEs to FDA as appropriate. The DCC will send an initial IDE safety report communication to the FDA within **2** business days of notification from the site. The DCC will submit a follow-up safety communication to the FDA, based on source documentation or PI Report from the site, within 10 business days from notification of a UADE for this IDE trial.

**Specific Adverse Event Definitions*****Allergic Reactions***

Allergic reactions can occur to the local anesthetic, sedatives, x-ray dye, heparin, protamine, or other agents administered during the procedure.<sup>23-29</sup>

***Arterial or Venous Injury***

Arterial or venous injury including arterial dissection, thrombosis, occlusion or hemorrhage at the catheter insertion sites or at other sites along the vessels (risk <1%).<sup>30-31</sup> This may result in hemorrhage, hematoma or ischemic injury to an extremity or major organ.

***Bleeding***

A bleeding event is defined by any one of the following:

- Transfusion of > 2 units RBC within the first 24 hours following ablation
- Death due to hemorrhage
- Re-operation for hemorrhage or tamponade

NOTE: Hemorrhagic stroke is considered a neurological event and not as a separate bleeding event.

***Major Infection***

A new clinical infection accompanied by pain, fever, drainage and/or leukocytosis that is treated by anti-microbial agents (non-prophylactic). A positive culture from the infected site or organ should be present unless strong clinical evidence indicates the need for treatment despite negative cultures. The general categories of infection are listed below:

***Sepsis***

Evidence of systemic involvement by infection, manifested by positive blood cultures and hypotension. In addition, we will record systemic antibiotic use for presumptive sepsis.

***Localized Infection***

Infection localized to any organ system or region, including the mediastinum, pericardium, or endocardium, without evidence of systemic involvement (see sepsis definition), ascertained by standard clinical methods and either associated with evidence of bacterial, viral, fungal or protozoal infection, and/or requiring empirical treatment.

***Occlusion of Coronary Artery***

Radiofrequency current or cryoenergy may cause occlusion of a coronary artery, either by direct thermal damage, spasm, or thrombosis (risk <0.5%).<sup>30-31</sup> Coronary arterial occlusion could produce myocardial infarction, angina or death. Should occlusion of a coronary artery occur for any reason, the physician will attempt to restore coronary blood flow through pharmacological, catheter and/or surgical intervention as medically indicated.

***Damage to AV Conduction System***

The application of radiofrequency or cryoenergy current close to the AV node or His bundle could damage or destroy the normal AV conduction system, producing complete heart block.

### ***Embolization of Thrombus***

The placement of linear lines of ablation may require a large number of RF lesions to be delivered to the left ventricle. The risk of stroke due to embolization of thrombus is approximately 1%. To minimize this risk, patients will be heparinized to an activated clotting time of greater than 300 seconds during the procedure.

### ***Cardiac Perforation***

Cardiac perforation may result from catheter manipulation or application of radiofrequency current or cryoenergy (risk is <1%).<sup>30-31</sup> This may result in cardiac tamponade and may require percutaneous pericardial drainage or surgical repair. Significant hemodynamic compromise can result in neurological injury or death. An increased risk of cardiac perforation may be associated with the use of saline-irrigated electrode catheter due to its creation of a larger, deeper RF lesion.

### ***Valvular Injury***

Injury to a cardiac valve may result from catheter manipulation or the application of radiofrequency current or cryoenergy (risk <1%).<sup>30-31</sup> This may produce valvular insufficiency and possibly require surgical valve replacement.

### ***Pulmonary Vein Stenosis***

While advances in technique and increased physician experience have made pulmonary vein stenosis unusual (risk 1.3%),<sup>30-31</sup> it may occur in patients who undergo catheter ablation.

### ***Radiation Exposure***

Radiation exposure during the fluoroscopic imaging of the catheters may result in an increase in the lifetime risk of developing a fatal malignancy (0.1%) or a genetic defect in offspring (0.002%).<sup>30, 31-33</sup>

### ***Pneumonia***

Rales, pulmonary edema, ARDS and asthmatic attack can be sequelae of aspiration pneumonia and nosocomial pneumonia. Aspiration of gastric contents can occur when subjects are intubated, and nosocomial pneumonia is well documented as the second most common nosocomial infection. The incidence of aspiration pneumonia and nosocomial pneumonia after AF ablation is rare (<1%).

### ***Phrenic Nerve Damage***

Phrenic nerve damage can be a sequela of pulmonary vein isolation; also rare (<1%) with RF catheter ablation.

***Cardiac Arrhythmias***

Any documented arrhythmia (excluding atrial fibrillation and atrial flutter) that *results in clinical compromise* (e.g., hemodynamic compromise, oliguria, pre-syncope or syncope) that requires hospitalization. Cardiac arrhythmias are classified as:

1. Sustained ventricular arrhythmia requiring defibrillation or cardioversion (either DC or chemical)
2. Cardiac conduction abnormalities requiring permanent pacemaker

***Pericardial Fluid Collection***

Accumulation of fluid or clot in the pericardial space that requires surgical intervention or percutaneous catheter drainage. This event will be subdivided into those with clinical signs of tamponade (e.g. increased central venous pressure and decreased cardiac output) and those without signs of tamponade.

***Pleural Effusion***

Accumulation of fluid or clot in the pleural space documented by chest radiogram or chest CT that requires evacuation with surgical intervention or chest tube placement.

***Heart Failure***

New onset of signs or symptoms of congestive heart failure *or* worsening of pre-existing heart failure by  $\geq 1$  NYHA class.

***Myocardial Infarction***

Myocardial infarction (MI) should be classified when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Under these conditions, any one of the following criteria meets the diagnosis for myocardial infarction.<sup>35</sup>

**Myocardial Infarction**

Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99<sup>th</sup> percentile of the upper reference limit (URL) together with evidence of myocardial ischemia with at least one of the following:

- Symptoms of ischemia;
- ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block [LBBB]);
- Development of pathological Q waves in the ECG;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

**Sudden unexpected cardiac death**, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumed new ST elevation or new LBBB, and/or evidence of fresh thrombus by coronary

angiography and/or autopsy, with death occurring before blood samples obtained, or at a time before the expected appearance of cardiac biomarkers in blood will be classified as a mortality due to MI.

### ***Atrioesophageal Fistula***

Atrioesophageal fistula is a rare (risk < 1%) but often fatal risk of RF catheter ablation.<sup>36-37</sup>

### ***Neurologic Dysfunction***

Any new, temporary or permanent, focal or global neurological deficit ascertained by a standard neurological examination (administered by a neurologist or other qualified physician and documented with appropriate diagnostic tests and consultation note). The examining physician will distinguish between a transient ischemic attack (TIA), which is fully reversible within 24 hours (and without evidence of infarction), and a stroke, which lasts longer than 24 hours (or less than 24 hours if there is evidence of infarction).

Each neurological event must be subcategorized as:

#### **Transient Ischemic Attack**

Defined as an acute event that resolves completely within 24 hours with no imaging evidence of infarction.

#### **Ischemic or Hemorrhagic Stroke (Cerebrovascular Accident)**

Defined as an event that persists beyond 24 hours or less than 24 hours associated with infarction on an imaging study. Hemorrhagic conversion of an ischemic stroke should be classified as ischemic.

#### **Toxic Metabolic Encephalopathy**

Defined as a disorder of the brain function that arises from abnormal systemic metabolism or exogenous substances, altering awareness and/or consciousness, in which there is a non-focal neurological examination and a negative brain image.

#### **Other Neurologic Dysfunction**

### ***Renal Events***

Two categories of renal events will be identified:

#### **Renal Dysfunction**

Abnormal kidney function defined as serum creatinine increase >50% or >0.3 mg/dl rise in serum creatinine (Cr) from baseline.

#### **Renal Failure**

New requirement for hemodialysis related to renal dysfunction. This definition excludes aquapheresis for volume removal alone.

***Respiratory Failure***

Impairment of respiratory function requiring re-intubation, tracheostomy or the inability to discontinue ventilatory support within 48 hours post-catheter intervention. This excludes intubation for re-operation or temporary intubation for diagnostic or therapeutic procedures.

***Arterial Non-CNS Thromboembolism***

An acute systemic arterial perfusion deficit in any non-cerebrovascular organ system due to thromboembolism confirmed by one or more of the following:

- Standard clinical and laboratory testing
- Operative findings
- Autopsy findings

This definition excludes neurological events.

***Venous Thromboembolic Event***

Evidence of venous thromboembolic event (e.g. deep vein thrombosis, pulmonary embolism) by standard clinical and laboratory testing.

***Other***

An event that causes clinically relevant changes in the patient's health, or any event that is life-threatening, results in a fatality, results in permanent disability, requires hospitalization, or prolongs an existing hospital stay.

As specifically related to the renal denervation procedure, additional potential adverse ANTICIPATED events that may occur include:

***Occlusion of Renal Artery***

Radiofrequency current may cause occlusion of a renal artery, either by direct thermal damage, spasm, or thrombosis (risk <0.5%). Renal arterial occlusion could produce renal infarction, acute renal failure, possibly resulting in the need for hemodialysis. Should occlusion of a renal artery occur for any reason, the physician will attempt to restore blood flow through pharmacological, catheter and/or surgical intervention as medically indicated.

***Renal Artery Stenosis***

Renal artery stenosis (defined as  $\geq 60\%$  reduction) by renal duplex ultrasonography will be defined as a i) renal-aortic ratio of 3.5 or more or a ii) peak systolic velocity of more than 200 cm/s.<sup>38-40</sup> Renal artery stenosis may also occur insidiously over time, and may not manifest until weeks after the ablation procedure. The risk of this is minimized by longitudinally staggering the ablation lesions such circumferential lesions are not placed in the same segment of the artery.

## 12. CLINICAL CENTERS

The study will be conducted in up to 20 sites both in and outside the United States. Each clinical center will be required to obtain IRB approval for the protocol and consent (and their revisions) in a timely fashion, to recruit patients, to collect data and enter it accurately in the electronic data capture (EDC) system, to faithfully follow the protocol and adhere to the standards of Good Clinical Practice (GCP). In addition, centers will be required to provide the DCC with the information necessary for interim, annual, and final reports, to provide source documents, data and regulatory documents for study monitors, provide prompt responses to DCC inquiries, and to participate in analyses and reporting of study results.

### **Investigator Profile**

All surgeons, cardiologists, coordinators and other investigators in the study must complete the Investigator Profile form, including hospital affiliation, address, telephone, fax, beeper and email information. The physicians and coordinators must email their CV, Conflict of Interest Statement and Financial Disclosure Certification, and Institutional Health Insurance Portability and Accountability Act (HIPAA) Certificates to the DCC.

### **Qualifications and Training**

Clinical investigators will be electrophysiologists with expertise in atrial fibrillation ablation. The certified operator will either perform the ablation and renal denervation on their own patient, or participate in the ablation and renal denervation of an enrolled patient. The clinical site Principal Investigator will be responsible for overseeing the ongoing performance of the other participating investigators at that site over the course of the study.

All clinical site investigators and coordinators will be trained by the DCC in the specifics of the protocol at a site initiation visit in advance of patient enrollment. In addition, the investigators and coordinators will undergo a separate training session to gain familiarity with the electronic data capture system.

### **Signature Verification**

Investigators will input an electronic signature into the electronic data capture system (EDC). It will be updated throughout the study as new site personnel are approved.

### **Conflict of Interest and Financial Disclosure Agreement**

This statement verifies that all investigators have no conflict of interest with any institution that may influence their participation in this study. All investigators need to complete this statement. Investigators will also submit a financial disclosure agreement.

### **Site Approval**

The following documents must be collected prior to site approval:

- Clinical Study Agreement
- Clinical site IRB roster
- Clinical site IRB approval, version and date for protocol and consent
- Clinical Center Laboratory Certification

A signed agreement between the clinical site and the DCC (Icahn School of Medicine at Mount Sinai) is required prior to site initiation. Prior to enrolling a patient, representatives from the DCC will conduct a site initiation for all investigators, coordinators, and any other health care professionals who may be involved in the study (e.g. engineers, social workers).

### **Patient Confidentiality**

All patients' records will be kept confidential according to HIPAA guidelines. Study Investigators, site Institutional Review Boards (IRBs), and the DCC may review source documentation as necessary, but all unique patient and hospital identifiers will be removed. The aggregate data from this study may be published as per publication policy documented in the trial agreements; however, no data with patient identifiers will be published.

## **13. SCREENING AND BASELINE DATA COLLECTION**

### **Pre-Screening Failure Form**

#### *Prior to informed consent*

Prior to approaching a patient to begin the informed consent process, the study personnel will review data on prospective patients to determine eligibility for inclusion in the trial. All pre-screened patients (patients who are not consented) who are not enrolled are recorded in the Pre-Screening Failure form. For these patients, reasons for failing the pre-screening process are documented. The data collected is HIPAA compliant and does not include patient identifiers but only includes screening quarter, screening year, age, gender and reason for not being eligible. The reasons for screening failure for patients who were consented are collected on the Eligibility Evaluation Form.

### **Consent**

#### *Prior to screening data collection and protocol-defined procedures (initiated $\geq 24$ hours prior to randomization)*

Prior to screening, a thorough explanation of the risks and benefits of the study will be outlined by the investigator to the patient and the patient will be asked to sign a consent form.

### **Release of Medical Information**

#### *Prior to screening data collection and protocol defined procedures*

The patient must sign the Release of Medical Information form or equivalent that authorizes release of medical records to the study investigators, monitors, and the FDA.

**Demographics Form***At initiation of screening*

A screened patient is defined as an individual (a consented patient) who was referred to, or identified at a clinical site for consideration of entry into the study, and for whom some preliminary (i.e. medical record) data have been collected and/or reviewed. For all patients screened, the first, middle, and last initial, date of birth, ethnic origin, and sex will be captured on the screening log and registration form. The EDC will generate a unique 8-digit identification code that will identify the patient throughout the course of the study.

**Medical History***Within 60 days prior to randomization*

This form captures the information pertaining to the medical history, including but not limited to previous myocardial infarction, myocardial revascularization, arrhythmias, automatic implantable cardioverter-defibrillator, permanent right ventricular or biventricular pacemaker, stroke and other comorbidities such as diabetes and peripheral vascular disease. Information regarding the current medical condition is also captured, including but not limited to disposition at time of screening (outpatient, inpatient, ICU monitoring, etc.).

**New York Heart Association Classification***Within 60 days prior to randomization*

Functional status will be assessed using the NYHA classification. NYHA classification will be determined by investigative center personnel and documented on the “New York Association Classification” form. The NYHA classification scheme is detailed in Appendix I.

**Medications***Within 60 days prior to randomization*

This form captures all medications taken within 30 days prior to randomization.

**Physical Examination***Within 60 days prior to randomization*

This form captures the comprehensive physical examination including vital signs cardiopulmonary examination, abdominal examination, and anthropometrics (height, weight and BSA).

**Quality of Life***Within 30 days prior to randomization*

AFEQT (Appendix II) Questionnaire will be completed by the patient and used to assess QoL. Data regarding completeness of QoL data collection and reasons for missing responses to questionnaires will be collected.

**Office Blood Pressure Measurement**

The auscultatory method of BP measurement will be used. Persons will be seated quietly for at least five minutes in a chair (rather than on an exam table), with feet on the floor

and arm supported at heart level. Caffeine, exercise and smoking will be avoided for at least 30 minutes prior to measurement. The bladder of the cuff will encircle at least 80 percent of the arm circumference. Three readings will be taken at intervals of at least 1 minute, and the average of those readings will be used to represent the patient's blood pressure. This approach is the standard approach recommended by JCN-7.<sup>41-42</sup>

### **Laboratory Assessment**

*Within 30 days prior to randomization*

- Hematology
- Coagulation
- Blood chemistry
- Liver function tests
- Glomerular Filtration Rate
- Urine or beta serum HcG (women of childbearing potential)

### **Eligibility Criteria/Eligibility Evaluation Form**

*Prior to randomization*

The inclusion and exclusion criteria will be documented by the clinical site study coordinator and verified with the site Principal Investigator in the Eligibility Evaluation Form. All screened patients (patients who are consented) who are not randomized in the trial will have the reasons for non-randomization documented in the Eligibility Evaluation Form. The data collected is HIPAA compliant and includes reason for not being randomized.

A representative from the DCC will be available to discuss any questions regarding patient eligibility.

### **Electrocardiogram (ECG)**

*Within 3 days prior to randomization*

An ECG will be done at baseline. This tracing will be used to assess heart rhythm on all patients and provide part of the documentation needed to establish the diagnosis of longstanding persistent AF.

### **Transthoracic Echocardiography**

*Must be performed within three months prior to randomization*

Transthoracic Doppler echocardiography will be used to measure LA function (a) atrial filling, (b) LA ejection fraction, (c) atrial systolic mitral annular velocity (TDI). MV function, mitral regurgitation and LV function and LV mass. The LV mass will be derived from 2D TTE imaging or MR imaging. Two-dimensionally guided M-mode echocardiography will be performed from a parasternal long-axis view. Using the leading edge-to-leading edge technique, the left ventricular end-diastolic dimension (LVED), posterior wall thickness, and interventricular septal thickness will be measured at end-diastole at the level just below the mitral valve leaflets. LV mass will be calculated using the following equation:  $0.8\{1.04[(LVED + \text{left ventricular posterior wall thickness} + \text{interventricular septal thickness}) - LVED]\} + 0.6$ . The LV mass index

will be calculated from this by dividing the LV mass by the height exponentiated to the power of 2.7.

## 14. POST-RANDOMIZATION DATA COLLECTION

### **Ablation Procedures**

#### *Initial catheter intervention and event driven*

Includes information regarding specific primary procedure, operative variables, device used for ablation, lesion sets created, additional procedures performed at time of initial operation, intra-operative pharmacological agents. The procedure form will also include a section where the investigator can depict the lesion set created by annotating a diagram; this form will be mailed/faxed to the DCC.

### **Hospitalizations**

#### *Index hospitalization and event driven*

For all patients the index (baseline) hospitalization and all subsequent hospital admissions (for any reason) must be reported on the Hospitalization form.

### **Patient Pre-discharge**

#### *Prior to discharge*

- **Medications**  
All cardiovascular medications are recorded.
- **Physical Examination (including vital signs and cardiopulmonary examination)**
- **Adverse Events**  
Detailed information regarding adverse events is recorded at the time an event occurs during hospitalization. Investigators are asked to make a judgment as to the seriousness and relationship of the event to the intervention.

### **Holter Monitoring**

#### *3, 6, 12 and 24 months.*

Prior to each time point, patients will be given a Holter device and instructed in its use.

### **Follow-up Visits**

#### *3 months ( $\pm 14$ days); 6 and 9 months ( $\pm 14$ days); 12, 18 and 24 months ( $\pm 30$ days)*

Follow-up visits will be conducted by investigative site personnel to document that the patient is alive and to assess the following:

- **7-day Holter Monitoring (3, 6, 12, 24 months only)**  
The Holter device provided to patients prior to each time point will be used for this assessment.
- **Laboratory Assessment (6, 12 months only)**
  - Blood chemistry

- ***Medications***  
All cardiovascular, inotropic, antiplatelet agents and anticoagulants will be recorded. Medications (including AADs) will be recorded at each follow-up, and also as indicated at the time of associated adverse events. We will also record response to DC cardioversions (success or failure; failure defined as the inability to restore sinus rhythm for  $\geq 30$  seconds post-electrical cardioversion<sup>20</sup>).
- ***Adverse Events, Anti-arrhythmic Interventions, and Hospitalizations***  
Patients will be asked to recall any adverse events (including stroke and bleeding) and the number of hospitalizations that occurred out of network since the previous contact. Patients will also be asked if they had a permanent pacemaker insertion, cardioversion or subsequent ablation since the last contact.
- ***Renal Doppler (6 months only)***  
All patients will undergo follow-up renal Doppler echocardiography at the investigative center. If the 6 month renal duplex ultrasonography indicates significant renal stenosis ( $\geq 60\%$ ) and/or image quality is inadequate to assess the severity of stenosis, than an MRI or CT should be performed as confirmatory testing.
- ***Transthoracic Doppler Echocardiogram (12 months only)***  
All patients will undergo follow-up transthoracic Doppler echocardiography at the investigative center (See Appendix III).

### ***Quality of Life***

The AFEQT questionnaire (Appendix II) will be used to assess QoL. The patients themselves must complete this questionnaire and return it to the investigative center.

- ***Functional Status***  
The NYHA class will be documented on the “New York Heart Association Classification” form.
- ***Adverse Events***  
Patients will be asked to recall any adverse events (including stroke and bleeding) and the number of hospitalizations that occurred out of network since the last contact. Patients will also be asked if they had a permanent pacemaker insertion, cardioversion or subsequent ablation since the last contact.
- ***Blinding assessment (12 months only)***  
Patients will be asked to determine which treatment(s) they believe they have received.
- ***Follow-up Treating Physician Blinding assessment (12 months only)***  
A patient’s follow-up treating physician will be asked to determine which treatment(s) the physician believes that the patient has received.

## **Event Driven Data Collection**

### ***Follow-Up Surgical Procedures***

#### *Event Driven*

All operations following the initial procedure(s) must be reported on the procedure form within 48 hours of the knowledge of the event. If the operation is to address a complication, the coordinator must also complete an adverse event report. All intra-operative transfusion requirements must be documented.

### ***Adverse Events***

#### *Event Driven*

Detailed information regarding adverse events will be recorded at the time an adverse event occurs. Investigators will be asked to make a judgment as to the seriousness and relationship of the event to the procedure using the guidance provided. All adverse events will be recorded until completion of the trial. All serious and all protocol-defined adverse events will be adjudicated by an EAC.

### ***Missed Visit Assessment***

#### *Event Driven*

If a patient is unable to attend any follow-up visit before the closure of a study visit window, a missed visit assessment must be completed that captures the reason for missing the follow-up.

### ***Mortality***

#### *Event Driven within 24 hours of knowledge of event*

The investigator will record the date of death, immediate cause of death, primary underlying cause of death, notation of autopsy being performed, and clinical narrative of the event.

### ***Study Completion/Early Termination***

#### *Event Driven or End of Study*

This form records the date and reason for study completion or early termination. The reasons for a patient to be withdrawn from this study at the patient's request or at the physician's discretion will also be documented on this form.

### ***Investigator's Statement***

#### *End of study*

The Principal Investigator will review all of the electronic case report forms (eCRFs) and patient summaries at that center. His/her electronic signature will attest to the accuracy and completeness of the data collected.

## **15. DATA MANAGEMENT**

All study data will be entered in the web-based electronic data capture (EDC) system (specified in detail in the operations manual). Study personnel requiring access will have their own Login/Password. Access to clinical study information will be based on individuals' roles and responsibilities. The application provides hierarchical user permission for data entry, viewing, and reporting options. For optimum security, the system operates Secure Socket Layer (SSL) 128-bit encryption protocol over Virtual Private Networks. This application is designed to be in full compliance with International Conference on Harmonization and Good Clinical Practices (ICH-GCP), the FDA's Code of Federal Regulations (CFR) Number 21 Part 11 Electronic Record and Electronic Signatures, the FDA's "Guidance For Industry: Computerized Systems Used in Clinical Trials", and the Privacy Rule of the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

### ***15.1 Quality Assurance***

The data quality assurance tool has been designed as an automatic feature of the EDC system. When a form is submitted the system conducts instantaneous validation and cross-form validation checks. A query is generated and sent to the site coordinator electronically so that data may be verified and corrected. All changes made to a form are stored in an audit log.

### ***15.2 On-Site Monitoring***

The primary objectives of the DCC in monitoring clinical sites are to educate, support, identify and resolve issues related to the clinical trial. The monitors will discuss the protocol in detail, and clarify any areas of uncertainty. At initiation of the study, the monitors will conduct a tutorial on the EDC system. The coordinators will practice entering data so that the monitors can confirm that the coordinators are proficient in all aspects of data entry, query response, and communication with the data management team.

The DCC will employ a risk-based approach to monitoring for this study. This will be accomplished via centralized or remote monitoring of data via the EDC with a focus on safety, study endpoints, data completion and data outliers. The DCC will also centrally monitor study logs including the Informed Consent Log, the Protocol Violation/Deviation Log and the Serious Adverse Event/IND Safety Report Log periodically to ensure that the sites are adhering to the study protocol and procedures. The DCC will generate performance metrics to analyze site characteristics such as recruitment rates and timeliness of data entry. This will allow the DCC to identify trends across sites and to address low-performing sites appropriately.

The DCC will also conduct one on-site monitoring visit each year for every clinical site for the duration of the study. In addition, interim monitoring will be conducted on an ongoing basis using the EDC system. During the annual on-site monitoring visits, the monitor will collect copies of any source documents (de-identified) for all deaths and AEs. Prior to each EAC meeting copies of any source documents (de-identified) requested by the DCC must be sent via FedEx or secure fax line to the DCC.

The monitors will review the source documents to determine whether the data reported in the EDC system are complete and accurate. They will also verify that all serious and protocol-defined adverse events exist on the source documents, are consistent with the protocol and are documented in the appropriate format. Source documents include medical charts, initial hospital admission reports, operative procedure records, discharge and re-admission reports, consult notes, radiology reports, lab reports, clinic records, and other study-related notes. The study monitors reserve the right to copy de-identified records in support of all adverse events and outcomes.

The monitors will also confirm that the regulatory (administrative) binder is complete and that all associated documents are up to date. The regulatory binder should include all revisions of the protocol and informed consent, IRB roster, IRB approvals for all of the above documents, IRB correspondence, investigator's agreements, CVs of all study personnel, institutional HIPAA certificates, monitor site visit log, telephone contact log, a study device log and correspondence with the DCC.

If a problem is identified during the visit (i.e., poor communication with the DCC, inadequate or insufficient staff to conduct the study, missing study documents, etc.), then the monitor will assist the site in resolving the issue. Some issues may require input from the Steering Committee or the Principal Investigator, as well as the sponsor.

The combination of yearly on-site monitoring and ongoing monitoring using the EDC system that includes instantaneous electronic validation, and visual cross-validation to detect complex errors, it is anticipated that the best possible quality and most complete data will be collected.

The monitor will verify a minimum of the following variables for all patients: initials, date of birth, sex, signed informed consent, eligibility criteria, date of randomization, anticoagulation, serious and protocol-defined adverse events, mortality, NYHA Classifications and QoL. These data will be 100% source data verified. All other data collection will be monitored as indicated by the data completeness and accuracy at each clinical site.

## **16. ANALYTICAL PLAN**

### ***16.1 Statistical Analysis Plan***

#### **General Design Issues**

This is a prospective, multi-center, double-blinded, randomized trial. Patients with hypertension and planning to undergo an AF ablation procedure will be randomized using a 1:1 allocation to either AF catheter ablation (usual therapy) or AF catheter ablation plus renal sympathetic denervation. Patients will be blinded to their group assignment (control vs. study group) throughout the duration of the study. The physician responsible for blood pressure management in the post-operative period (who will not be the same as the operator who performed the procedure) will also be blinded to group assignment. The

operator performing the procedure will not be blinded to the treatment. Outcomes will be assessed and recorded by study personnel masked to treatment assignment. The trial's primary goal is comparing two treatment arms: an AF ablation control and AF ablation + renal sympathetic denervation study group. The null hypothesis of principal interest is that there will be no difference through 12 months between the two treatment arms in single-procedure freedom from AF off of all AADs after a 90 day blanking period. There are a number of secondary objectives, including 1) assessing the 24-month single procedure freedom from AF off of all AADs after a 90 day blanking period; 2) measuring the impact of arrhythmia event reduction on Quality of Life, and 3) other surrogate measures of potential benefit from renal denervation (such blood pressure differences, differences in LV mass and the number of anti-hypertensive medications at study end).

## Sample size

### *16.2 Randomization Design and Procedure*

This trial will randomize a total of 300 patients in equal proportions to AF ablation with renal sympathetic denervation versus AF ablation alone. The randomization will be stratified by clinical center and use a random permuted block design, with blocks of size 4 or 8 chosen at random. Randomization will be implemented as described in section eight. A total of three hundred patients provides 80% power to detect a relative 40% decrease in the one-year incidence of atrial fibrillation (from 40% to 24%) in patients treated with AF ablation with renal sympathetic denervation compared to AF ablation alone based on a two-tailed 0.05 level chi-squared test. The sample size accounts for two planned interim analyses.

This study is divided into two phases: a PILOT phase (to include 50 patients) followed by the remaining 250 patients to a total of 300 patients. The PILOT phase will be conducted at up to 10 US sites: TBD. An interim safety analysis will be conducted when all patients in the PILOT phase (50 subjects) have completed the 3-month follow up visit. The purpose of this analysis is only for safety. The efficacy/outcome data for the primary endpoint will not be examined; this will permit pooling these 50 patients with the subsequent 250 patients for the final efficacy analysis.

### *16.3 Data Monitoring and Analysis*

#### **Methods of Analysis**

The primary efficacy outcome of this randomized clinical trial is single procedure freedom from AF over 12 months post randomization, excluding a 90 day blanking period. Patients who die within 12 months will be considered treatment failures (not free of AF). The null hypothesis is that there is no difference in the proportion of patients meeting the primary outcome between patients randomized to AF ablation plus renal sympathetic denervation or AF ablation alone. That is, we will test

$$H_0: \pi_0 = \pi_1 \text{ versus } H_1: \pi_0 \neq \pi_1$$

where  $\pi_0$  and  $\pi_1$  represent the proportion free from AF at 12 months assessment (following a single AF ablation procedure and off AADs after 90 days) among patients randomized to receive either AF ablation plus a single renal sympathetic denervation procedure or AF ablation alone. The primary null hypothesis will be tested in an intent-to-treat analysis at the 0.05 level. To compare the proportion of patients free from AF in the two treatment groups, we will use a mixed model in which the type of catheter is considered as a random effect to account for the heterogeneity that could be brought about by the use of different catheters. The benefit of AF ablation plus renal sympathetic denervation to AF ablation alone will be quantified by the relative risk and associated 95% confidence interval (adjusted for two interim looks).

Patients who die prior to the 12-month assessment, or who are determined by an independent adjudicator to be too ill to undergo AF measurement, will be considered as treatment failures (not free of AF). In the primary analysis, patients in both treatment arms who undergo ablation therapy for AF subsequent to the index procedure will be considered treatment failures (not free of AF). Patients missing the 12-month assessment, for reasons other than death or illness, will have their primary outcome imputed using a multiple imputation algorithm described below. Imputed data will be rounded to 0 (free of AF) or 1 (AF present).

An implicit assumption of the proposed primary analysis is that the results for all of the study centers can be pooled or combined. We will assess the validity of this assumption by a variety of means, recognizing that establishing poolability merits both clinical and statistical examination.

We do not anticipate that pooling of results across study centers will be threatened due to any clinically important differences in trial conduct. Centers participating in the study have been selected for their experience and demonstrated success in conduct of clinical trials and adherence to study protocols. Frequent site monitoring and regular contact including teleconferences involving site coordinators and investigators, as well as in person meetings, ensure that all centers strictly follow trial protocols.

Additionally, we will conduct several statistical analyses to assess poolability of results across centers. These include center specific analyses of the primary endpoint to assess the consistency of results, and similarity of patient demographics and baseline characteristics across centers. In addition to uncovering potential poolability issues that would require further exploration, differences may indicate the need for additional, more complex, statistical analysis. The effect of center will be explicitly assessed by a secondary analysis testing the interaction of treatment with center via a logistic regression model incorporating centers through a series of indicator variables. Power for detecting an interaction may be low, so we will use a p-value of 0.15 to assess interaction, and also consider the qualitative analysis of center specific results to assess the extent the heterogeneity of treatment by center.

## **Interim Analysis**

We plan to perform two interim analyses with respect to the primary outcome to give the option of stopping early should results strongly favor one arm or the other. The proposed timing of the two analyses is at 0.33 and 0.67 on the information scale, i.e., after 33% and 67% of patients reach the primary endpoint. The utility of performing these analyses will depend on the rate of accrual of patients into the trial. A group sequential procedure allows for flexibility in the number and timing of interim analyses should the DSMB choose to modify the proposed plan, or should accrual mitigate the usefulness of an interim look. We will use the Lan-DeMets approach, implementing an O'Brien-Fleming-type spending function that allots most of the type I error to the final look.<sup>43</sup>

In addition to the ethical concern of continuing a trial that shows a clear benefit in favor of one treatment, there is also a corresponding ethical concern of continuing a trial that has little chance of ever showing a benefit of one treatment compared to the other. We propose that the trial's conditional power, under the original alternative hypothesis, be computed at the interim look and that the DSMB use this as a basis to determine whether randomization, if not completed, be halted for futility. We propose that consideration be given to halting the trial for futility if, given the data up to the point of the interim analysis, the probability of detecting an absolute 16% benefit for patients randomized to AF ablation + renal sympathetic denervation is less than 40%.

In addition an initial safety review will be performed after 40 patients have been enrolled and ablated. The proposed analysis after 40 patients have been ablated will only assess safety concerns. The results of this analysis, a summary and comparison of adverse events by treatment arm, will be provided to FDA for review. We propose to continue enrollment during this period of FDA review, up to a maximum of 80 patients. If 80 patients have been randomized, and FDA has not concluded its review, enrollment would cease pending FDA approval for study continuation. No study modifications are proposed based on this initial review.

### **Assessment of Balance of the Randomization**

The success of the randomization procedure in balancing important covariates between randomization groups will be assessed at the interim analysis and at the final analysis. Continuous measures will be compared using t-tests, while chi-squared tests will be used to compare categorical variables such as age and ethnicity. As 300 patients will be randomized, no substantial imbalances are expected. However, should any covariate differ significantly between treatment groups at the 0.01 level, and be substantively large, we will adjust for those covariates in all analyses. Additional sensitivity analysis will be employed to determine the effect on the trial's primary analysis result when adjusted for any covariate found to differ between groups at the 0.15 level.

### **Secondary Analyses**

A number of secondary analyses are planned to supplement the primary analysis. Comparisons will be based on chi-squared test for categorical variables and t-tests for continuous variables. Incidence rates of any serious adverse event will be compared using Poisson regression. These secondary analyses will be performed at a two-sided 0.01 level.

- ***Compare AAD-free single-procedure freedom from AF recurrence at 24 months (not-including recurrences within the first 90 days of the initial ablation procedure)***
- ***Compare freedom from AF recurrence at 24 months regardless of AAD use (excluding the 90 day blanking period)***
- ***Examine blood pressure control between the two groups as compared to baseline, 6 months, 12 months and 24 months***
- ***Compare Major adverse cardiac events (MACE)***
  - defined as a non-weighted composite score of: death, stroke, CHF hospitalization, clinically diagnosed thromboembolic events other than stroke and hemorrhage requiring transfusion within 12 months of randomization
- ***Serious Adverse events***

Demographic, baseline, and outcome characteristics will be summarized numerically and graphically. For continuous variables numerical summaries will include the mean, standard deviation, median, inter-quartile range and range. Graphical summaries will include histograms and box plots. Categorical variables will be summarized by observed frequency distributions and bar graphs. Clinical reports will provide summaries by clinical sites, and by region (U.S. versus Europe). Additional descriptive analyses include:

#### ***Anti-arrhythmic Interventions***

In addition to use of AADs after 90 days post-randomization, anti-arrhythmic interventions include the requirement for permanent pacemaker placement, electrical cardioversion, and any AF ablations (surgical or percutaneous) at any point following the treatment intervention. We will compare the need for anti-arrhythmic interventions between treatment groups.

#### ***Anti-hypertensive medication use in the two treatment arms at 24 months***

#### ***Measures of LV hypertrophy (LV wall thickness, mitral inflow parameters) and LA size by TTE at baseline and at 12 months for each patient***

#### ***Procedure related adverse events (Safety)***

Differences in the incidence of individual protocol-defined and serious adverse events within 24 months of randomization will be summarized using exact 95% confidence intervals (based on the Poisson distribution) for the risk ratios for individual adverse events for treatment with AF ablation with renal sympathetic denervation versus treatment with AF ablation alone will be computed.

### ***Quality of Life***

Compare quality of life between treatment arms and differences in quality of life from baseline using a disease specific scale (AFEQT) at 12 and 24 months.

### ***Mortality***

Survival will be assessed by all-cause mortality at 24 months. The proportion of deaths between randomization groups will be primarily compared by a continuity-corrected chi-squared test. Time to death will also be described by Kaplan-Meier curves and differences between randomization groups will be assessed via the log-rank test.

### ***Analysis of other Atrial Fibrillation Endpoints***

#### **Imputation Procedure for Missing Data**

Randomized patients missing the primary efficacy endpoint is a potential problem in all clinical trials. Adherence to the intention-to-treat principle requires that all randomized patients be included in the primary analysis. We will report reasons for missing data for each randomization group and compare the reasons qualitatively. The effect that any missing data might have on results will be assessed via sensitivity analysis of augmented data sets (for example, best-case or worst-case scenarios). Patients missing the trial's primary endpoint will be included in the analysis by modern imputation methods for missing data.

Data imputation methods generally require several assumptions to support their validity theory. One such assumption is that data are missing at random<sup>45</sup>, i.e., the missing nature of the variable is independent of value of the variable given the observed data. While it is not possible to explicitly verify assumptions about the missing data mechanism, it may be possible to detect when data are not missing at random. If there is no evidence that the data are not missing at random, the imputation method described below will be implemented. If the assumption of missing at random appears untenable, then additional procedures including selection modeling and pattern mixture modeling will be considered.

The main feature of the imputation approach is the creation of a set of clinically reasonable imputations for the respective outcome for each dropout. This will be accomplished using a set of repeated imputations created by predictive models based on the majority of participants with complete data. The imputation models will reflect uncertainty in the modeling process and inherent variability in patient outcomes, as reflected in the complete data. The specific imputation model to be used will be specified prior to the examination of any outcome data.

After the imputations are completed, all of the data (complete and imputed) will be combined and the analysis performed for each imputed-and-completed dataset. Rubin's method of multiple (i.e., repeated) imputation will be used to estimate treatment effect.

We propose to use 15 datasets (an odd number to allow use of one of the datasets to represent the median analytic result). A tipping point analysis will also be performed.

These methods are preferable to simple mean imputation, or simple “best-worst” or “worst-worst” imputation, because the categorization of patients into clinically meaningful subgroups, and the imputation of their missing data by appropriately different models, accords well with best clinical judgment concerning the likely outcomes of the dropouts, and therefore will enhance the trial’s results.

### ***Crossovers***

Crossovers (patients who after randomization switch from the allocated treatment to the non-allocated treatment) are not expected to occur in this trial, given the nature of the interventional therapy.

## **17. ORGANIZATION OF THE STUDY**

### **Event Adjudication Committee**

The charge of the Event Adjudication Committee (EAC) is to review source documents and adjudicate all adverse events and causes of mortality. The individuals who will serve on the committee are unaffiliated with the clinical sites and the DCC, and will be appointed by the DCC. The committee will consist, at least, of a statistician, a cardiologist, and a nephrologist. The EAC will meet every 6 months or as needed to review outcomes data for each subject enrolled.

### **Data and Safety Monitoring Board**

To meet the study's ethical responsibility to its subjects, an independent data safety monitoring board (DSMB) will monitor results during the study. The board consists of physicians and a biostatistician who have no formal involvement or conflict of interest with the subjects, the investigators, or the DCC, and will be appointed by the Executive Steering Committee. The DSMB will act in a senior advisory capacity to the DCC regarding data and safety matters throughout the duration of the study. In addition, the DSMB will review interim summary results of the accumulating data from the Event Adjudication Committee every 6 months. These data include adverse events (e.g., infection, bleeding, right heart failure) and mortality. They will communicate their findings directly with the DCC. The FDA will be provided a copy of any written communication from the DSMB to the study sponsor related to safety concerns, or changes to the study protocol, procedures or informed consent document. The DSMB will be provided a copy of any letter from the FDA to the study sponsor related to safety concerns, or changes to the study protocol, procedures or informed consent document. The clinical centers will have no contact with the members of DSMB regarding this trial and no voting member of the committee may participate in the study as an investigator. Non-DSMB members will not be allowed during DSMB closed meetings.

**Data Coordinating Center**

A university-based DCC bears responsibility for study design, monitoring interim data, and analyzing the study's results in conjunction with the investigators. The DCC will coordinate and monitor the trial. The DCC will administrate the DSMB and EAC.

**Electrophysiology Core Lab**

All Holter rhythms will be centrally analyzed by the Helmsley Electrophysiology Center Core Lab directed by Joseph Anthony Gomes, MD, located at the Icahn School of Medicine at Mount Sinai, New York, NY.

**Executive Steering Committee**

The Executive Steering Committee (with the assistance of the protocol development committee) will provide the overall scientific direction for the study. The responsibilities of the Steering Committee are to: (a) maintain contact with study investigators to ensure high quality data collection; (b) approve and implement major protocol changes in response to advice from the DSMB; (c) collaborate in data analysis, interpretation, and publication; (d) establish criteria for authorship on all manuscripts, publications and presentations that arise from the study.

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### Appendix I: New York Heart Association Classification (NYHA)

Class	Patient Symptoms
Class I (Asymptomatic)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

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## Appendix II: Quality of Life Measures

### Atrial Fibrillation Effect on Quality-of-life (AFEQT) Questionnaire

**Section 1. Occurrence of atrial fibrillation**

Name or ID: \_\_\_\_\_

Are you currently in atrial fibrillation?  Yes  No

If **No**, when was the last time you were aware of having had an episode of atrial fibrillation? (Please check one answer which best describes your situation)

- |                          |  |
|--------------------------|--|
| __ earlier today         | __ 1 month to 1 year ago                           |
| __ within the past week  | __ more than 1 year ago                            |
| __ within the past month | __ I was never aware of having atrial fibrillation |

**Section 2. The following questions refer to how atrial fibrillation affects your quality of life.**

On a scale of 1 to 7, over the past 4 weeks, as a result of your atrial fibrillation, how much were you bothered by: (Please circle one number which best describes your situation)

	Not at all bothered Or I did not have this symptom	Hardly bothered	A little bothered	Moderately bothered	Quite a bit bothered	Very bothered	Extremely bothered
1. Palpitations: Heart fluttering, skipping or racing	1	2	3	4	5	6	7
2. Irregular heart beat	1	2	3	4	5	6	7
3. A pause in heart activity	1	2	3	4	5	6	7
4. Lightheadedness or dizziness	1	2	3	4	5	6	7

On a scale of 1 to 7, over the past 4 weeks, have you been limited by your atrial fibrillation in your: (Please circle one number which best describes your situation)

	Not at all limited	Hardly limited	A little limited	Moderately limited	Quite a bit limited	Very limited	Extremely limited
5. Ability to have recreational pastimes, sports, and hobbies	1	2	3	4	5	6	7
6. Ability to have a relationship and do things with friends and family	1	2	3	4	5	6	7

On a scale of 1 to 7, over the past 4 weeks, as a result of your atrial fibrillation, how much difficulty have you had in: (Please circle one number which best describes your situation)

	No difficulty at all	Hardly any difficulty	A little difficulty	Moderate difficulty	Quite a bit of difficulty	A lot of difficulty	Extreme difficulty
7. Doing any activity because you felt tired, fatigued, or low on energy	1	2	3	4	5	6	7
8. Doing physical activity because of shortness of breath	1	2	3	4	5	6	7
9. Exercising	1	2	3	4	5	6	7
10. Walking briskly	1	2	3	4	5	6	7
11. Walking briskly uphill or carrying groceries or other items, up a flight of stairs without stopping	1	2	3	4	5	6	7
12. Doing vigorous activities such as lifting or moving heavy furniture, running, or participating in strenuous sports like tennis or racquetball	1	2	3	4	5	6	7



### **Appendix III: Transthoracic Doppler Echocardiography**

Transthoracic Doppler echocardiography will be used to measure LA function (a) atrial filling, (b) LA ejection fraction, (c) atrial systolic mitral annular velocity (TDI). MV function, mitral regurgitation and LV function and LV mass. The LV mass will be derived from 2D TTE imaging or MR imaging. Two-dimensionally guided M-mode echocardiography will be performed from a parasternal long-axis view. Using the leading edge-to-leading edge technique, the left ventricular end-diastolic dimension (LVED), posterior wall thickness, and interventricular septal thickness will be measured at end-diastole at the level just below the mitral valve leaflets. LV mass will be calculated using the following equation:  $0.8 \{1.04[(LVED + \text{left ventricular posterior wall thickness} + \text{interventricular septal thickness}) - LVED]\} + 0.6$ . The LV mass index will be calculated from this by dividing the LV mass by the height exponentiated to the power of 2.7.

## **Appendix IV: Study Sites**

Icahn School of Medicine at Mount Sinai  
Massachusetts General Hospital  
Na Homolce Hospital  
Medical University of South Carolina  
Others to be determined

## **Appendix V: List of Recommended Atrial Fibrillation Ablation Devices**

Biosense Webster Celsius Thermocool Ablation Catheter  
Biosense Webster Celsius Thermocool SF Ablation Catheter  
Biosense Webster Navistar Thermocool Ablation Catheter  
Biosense Webster Navistar Thermocool SF Ablation Catheter  
Biosense Webster Thermocool Smarttouch Ablation Catheter  
Medtronic Arctic Front Cryoballoon Ablation Catheter  
St Jude Medical Tacticath Ablation Catheter  
CardioFocus HeartLight Ablation Catheter